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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/037,243	FREIMUTH ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-60,62-64 and 87-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-60, 62-64 and 87-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

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DETAILED ACTION

Receipt is acknowledged of a response, filed 05/02/05. All amendments to the claims are entered. Claims 1-52, 61 and 65-86 are cancelled and new claims 87-93 are added. Thus, claims 53-60, 62-64 and 87-93 are currently pending and under consideration in this action.

All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections repeated herein. As new grounds of rejection are set forth, this action is NON-FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 53-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

This is a new ground of rejection that is not necessitated by amendment to the claims. However, the grounds of rejection are applicable to claims 53-60 as discussed herein. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. More particularly, the claims are directed to a genus of peptide extensions of 61 or fewer amino acids having a net negative charge (-2 to –20)

under physiological conditions. This is a genus claim in terms of nucleic acids encoding peptide extensions of *any* number of amino acid residues between 1 to 61 having a net negative charge of between –2 and –20 under physiological conditions, which must correspond to the functionality of enhanced solubility and folding in a physiological environment, when linked to *any* protein.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966). To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("The description must clearly allow persons of ordinary skill in the art to recognize that (the inventor) invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious" and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966. Further, the Guidelines for Written Description state:

> "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). Futhermore, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph).

The critical essential elements as defined by the claimed genus consist of nuclei acids encoding *any* peptide extension having 1 to 61 amino acid residues linked to *any* protein, wherein the extension has a negative charge of –2 to –20 under physiological conditions and *any* protein expressed therefrom exhibits enhanced solubility and proper folding.

The specification clearly teaches that there is no common structural characteristic that can be identified that corresponds to the requisite functionality. Indeed, even with respect to a single embodiment within the genus of nuclei acids, it becomes clear that the species encompassed by the claimed genus are not interchangeable. For example, where the 57 amino acid residue T7B peptide extension is expressed in yeast, there is unpredictability as to whether a particular protein when expressed exhibits enhanced solubility. (e.g., Specification, p. 46, Table 2). The level of unpredictability can only be exacerbated by the tens of thousands of different embodiments that are possible when linking peptide extensions of varying sizes and of varying amino acid sequence to proteins of varying sizes and varying amino acid sequences and expressing said proteins under physiological conditions in cell.

Given the enormous breadth of the structures/activities encompassed by the rejected claims, and given the limited description from the instant specification of such structures as correlated to having any activity, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to describe the broadly claimed genus. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

2. **Claims 53-60, 62-64 and 87-93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding 57 amino acid residue T7B peptide linked to the carboxy terminal of a protein of interest under physiological conditions and enhancing the protein's solubility and proper folding in *E. coli*, does not reasonably provide enablement for any peptide extension of 1 to 61 amino acid residues having a –2 to –22 net negative charge linked to any target protein and expressed in any host to enhance protein folding and solubility when expressed in any cell.**

This rejection is of record, repeated herein and applied to the claims insofar as the claims exceed the allowable scope, including the new claims. The rejection is modified so as to reflect the amendment to the claims. A response to Applicant's arguments is set forth below, immediately following the body of this rejection. (Infra, Response to Arguments).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The test for enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims' scope is both wide and deep. The claims are directed to expression vectors comprising any peptide extension having a net negative charge between –2 and –22 and being from 1 to 61 amino acid residues, where the peptide extensions is linked to any protein of interest of any size or sequence, where the fusion proteins are expressed in any host, physiological conditions and expression results in enhanced protein folding and solubility.

Nature of the invention. The invention is directed protein expression vectors. The only disclosed utility for the vector compositions is directed to expression of target protein to ensure proper folding and enhanced solubility based on fusion protein technology, particularly to preclude inclusion body formation, as a result of incorporating a peptide extension that inheres a net negative charge. In essence, the peptide extension can be thought of as a "solubilizing partner".

State of the art/Unpredictability of the art. The state of the art of protein production is somewhat developed in regard to particular host organisms, e.g. *E. coli*. Indeed, even with regard to *E. coli* based protein expression, many fundamental aspects of physiology remain to be uncovered and will affect progress in optimizing this bacterium for protein expression. (e.g. Baneyx, F. Curr. Opin. Biotech. 1999; 10:411-421, p. 418, col. 2). However, there are vagaries as to protein production that often require considerable, costly and lengthy experimentation, each of which would necessarily be exacerbated for host organisms for which there is little knowledge in the art with respect to recombinant protein production.

Attaching any sized peptide extension, fused to a target protein of any size would not necessarily result in expression or enhanced folding/solubility in any host organisms. For

example, even within well characterized systems, such as in *E. coli*, expression of larger proteins in a cell is often inefficient or unsuccessful, particularly as the protein of interest or expressed protein in general increases in size or is smaller but a multi-domain protein. (e.g. Frydman, J. Annu. Rev. Biochem. 2001; 70:603-47; p. 621, ¶ 2; present in IDS, thus a copy is not being submitted herewith). Furthermore, depending on the size of the target gene encoding the target protein, a vector may not even be available to effectuate protein expression. In the same vein, the vector used may become unstable in a particular cell type, or the encoded protein may be toxic to a particular host, resulting in vector loss, thus no protein expression. (e.g. Baneyx, F. Curr. Opin. Biotech. 1999; 10:411-421, p. 411, col. 2). Arguendo, even if such unpredictability for a particular host such as *E. coli*, could be worked out with routine experimentation, such is not necessarily the case for any cell system. Furthermore, with respect to fusion protein technology to enhance proper folding, to preclude inclusion body formation, all fusion partners for a particular target protein will not equally alleviate inclusion body formation. (Id. p. 471, ¶ 1). Ironically, increased solubility for a particular fusion protein may itself lead to product aggregation as more of the protein would accumulate intra-cellularly, which in turn can lead to inclusion body formation. (e.g. Swartz, JR. Curr. Opin. Biotech. 2001; 12:195-201, at 201, col. 2, ¶, 4). In addition, even with proper folding, the fused protein may not contain native target protein activity, due to formation and isomerization of disulfide bonds, which itself can depend on the host cell or the size and number of protein domains.

Regarding protein expression, an area of unpredictability may be mRNA stability or even more importantly translation initiation, which could differ, based on the size of the fusion protein (whether through variability in the extension or the target protein), or based on the type of cell

species/strains being used. (See generally, Swartz, JR. Curr. Opin. Biotech. 2001, at pp. 196-7; noting mRNA secondary structure can block ribosome binding caused significant decrease in expression). Importantly, in regard to enhancing proper folding to preclude inclusion body formation, "Finding the optimal refolding conditions is still relatively empirical, with the best results obtained from evaluating a matrix of conditions affecting solubility and disulfide-bond formation and isomerization."[1] (Id. at p. 197, col. 2, last ¶). With respect to the target protein size and characteristics affecting protein folding, thus production, solubilizing partners do not always preclude inclusion body formation, thus enhance solubility. (Thomas et al. Appl. Biochem. Biotech. 1997, 66:197-238; p. 201, ¶ 2). While the "partners" studied in the art may not be the same peptide extensions as in instant application, the salient analogous point is, that while a fusion construct does aid in proper folding/solubility for one protein, it does not necessarily do so for any protein in any cell system.

Amount of guidance provided. The specification provides prophetic guidance as to expression of proteins in any host cell and indicates that any size peptide extension can be used, where the extension having has the prescribed negative charge deemed necessary to provide enhanced solubility/folding. (e.g. Spec. p. 18, ¶ 2). The specification does not provide any guidance as to what would be the size limitations for the peptide extensions, target proteins relative to particular vectors (i.e. vector loss/maintenance) or other cells whether eukaryotes or prokaryotes. Nor does the specification contemplate differentials in regard to temperature or pH, for example, in different cellular hosts, in effecting the charge characteristics for peptide extensions.

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[1] This exemplifies unpredictability in the art, not that the *best* conditions for practicing the invention are required.

Number of working examples. The specification provides three peptide extensions (i.e. T7A, T7B and T7C, or SEQ ID NOs: 6 and 5), which are shown to enhance solubility of the a single target protein – CAR D1 – where protein expression is induced in *E. coli* cells, at 25° and 37° C. (Spec. pp. 27-29; showing expression of CAR D1-T7B and -T7C fusion proteins).

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of working examples commensurate with the scope of the claims, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention commensurate with the scope of the claims.

Response to Arguments

Applicant's arguments have been considered in full but are not deemed persuasive. Applicant's arguments are separated based on the Wand's factors analysis. Thus a response to the arguments is set out accordingly herein below.

Applicant asserts that the amendment to the claims narrow the scope of the invention so that the claims are supported by the specification, where the size of the peptide extension is narrowed to between 1 to 61 residues and the function is defined as enhancing protein solubility and native protein folding. (e.g., Remarks, p. 18, bottom half). In essence, with respect to peptide extensions linked to target proteins, Applicant suggest that given the narrowing amendments, one of skill will have sufficient knowledge to express proteins of varying sizes/sequence in any cell expression system. (Remarks, p. 18, last ¶ bridging to p. 19).

As to expression in any cells, Applicant asserts that regardless of the host cell proper folding and solubility would be expected since expression is under physiological conditions. (Remarks, p. 19, ¶ 2).

While the peptide extensions are narrowed in size (claims 53-60), as well as in function (claims 53-60 and 62-64, 90-93), the claims remain broad in breadth and depth. With respect to claims 53-60 the claims are directed to any peptide sequence having the requisite negative charge and linked to any protein. Furthermore, the corresponding functionality of enhancing solubility and protein folding is expected from expression in any cell. As to claims 62-64 and 90-93 the peptide extensions are limited to T7B or SEQ ID NO: 6 (elected species), but the claims' scope remains broad insofar as the extension is linked to any protein, whereby expression in any system under physiological conditions results in enhanced solubility and protein folding. In sum, the claims remain broad in scope.

With respect to unpredictability and state of the art, Applicant asserts that determinations related to selection of a peptide extension, a target protein and an expression system are not at all difficult, lengthy or costly. (Remarks, p. 21, top; citing commercial organizations providing testing for various expression systems). In essence Applicant's assertions can be summarized to stand for the proposition that protein expression utilizing the invention will involve nothing more than routine experimentation. (e.g., p. 22, ¶¶ 2-4; p. 23, ¶ 2, last line; p. 24, top ¶). Indeed, Applicant concedes that attaching any peptide extension fused to any target protein is unpredictable with respect to enhanced solubility/protein folding, but implies that any negative extension of 61 or fewer amino acid extension is not. (Remarks, p. 21, last ¶).

Thus, it appears Applicant does not contest that experimentation is necessary to assess whether the thousands of possible combinations of various proteins/extensions and cell systems will result in enhanced solubility and native protein folding. Furthermore, Applicant appears to concede that there is a level of unpredictability in linking a particular peptide extension to particular proteins to elicit the desired effects. (e.g., Remarks, p. 22, last ¶; noting that T7B linked to various proteins and expressed in *E. coli* resulted in some proteins exhibiting enhanced solubility/protein folding, while others did not). Then, it seems evident that the only issue is whether such experimentation is undue or merely routine, as Applicant asserts. Before proceeding further, Applicant's assertion that RNA stability and plasmid loss are not relevant to the instant invention is accepted and such grounds of unpredictability are withdrawn.

The level of experimentation exceeds the bounds of merely routine steps, because even within the narrower scope of claims 53, 62 or 90, the potential number of combinations of nucleic acids encoding fusion proteins is limited by the following: (1) number of potential peptide extensions having up to 61 amino acid residues in their sequence and a net negative charge of –2 to –22 under physiological conditions (independent claim 53); (2) number of said extension linked to any protein (claim 53) or T7B extensions linked to any protein (claims 62 and 90); (3) number of expression systems/host cells (all claims). Thus, the sheer number of potential combinations reaches enormous proportions. However, even for a single peptide extension, Applicant's own teaching exhibit that expression of 5 out of 13 proteins (at 25 Celsius) does not result in enhanced solubility and protein folding. Thus, it seems given the claims encompass tens of thousands of embodiments, that the number of embodiments that are inoperative are quite large.

"Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." (*Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414). Therefore, the artisan could not simply examine a single peptide extension embodied by the claims and examine a particular protein of interest and determine whether the resulting fusion can be expressed with the expected functionality of enhanced solubility and protein folding.

Furthermore, while certain expression systems are widely used for protein expression/production (e.g., *E. coli*, *S. cerevisiae*, *P. pastoris*), such skill and knowledge does not translate into predictability with respect to any expression system. Applicant asserts that since expression is under physiological conditions, then the selection of the host cell system is of little moment. However, depending on the system, and notwithstanding that expression is in the cytosol, expression of proteins can be dependent on a multitude of stress reactions in the cell. For example, one of skill will recognize that metabolic stresses imposed upon the host cell by the expression of a recombinant protein will largely influence productivity of overexpression for a given protein. (e.g., Mattanovich et al. J. Biotech. 2004; 113:121-135; generally discussing the vagaries of protein overexpression in yeast cells). For example, for a given protein of interest, the artisan might have to undertake codon optimization for a given host cell, then link the codon optimized protein to various test peptide extensions, then express the fusion protein only to discover overexpression (i.e., enhanced solubility/protein folding) does not result. Thus, the same experimental steps would have to be repeated for another host cell system. Now multiply these steps by the number of potential peptide extensions and number of potential target proteins.

Indeed Applicant appears to suggest that selection of cell type is not a mere remedial step. (Remarks, p. 31, last ¶; indicating solubility profiles resulting in bacterial cells cannot be readily translated to results in other cell types such as yeast, insect or mammalian cells).

Further, that such steps/experimentation can be outsourced, as Applicant suggests, does not obviate the fact that the level of experimentation is excessive and undue. (Remarks, p. 21, middle; indicating that commercial entities are available that provide tools for testing and using various expression systems). Applicant also asserts that vectors encoding solubility enhancement tags (SET) are provided from such commercial sources. (citing Attachment A; comprising the *VariFlex™ Bacterial Protein Expression System*, Stratagene Catalog; hereinafter Catalog). However, the expression vectors disclosed are not amenable to use in any cell system. Furthermore, the peptide extensions are limited to three SETs, which correspond to T7B tags of instant SEQ ID NOs: 6, 12 and 14. Indeed, the Catalog makes explicit the point that "Since every protein is unique, the optimal SET tag needs to be determined empirically for each protein of interest." (Catalog, p. 8, ¶ 2; cross-reference: Attachment A, p. 39). Thus, even for the three extensions, SET1, SET2, SET3 dislcosed therein, the number of potential nonenabled embodiments is only limited by the number of proteins of interest.

It should be made clear that, the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. "Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404; *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the

first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification)." *In re Wright* (CAFC) 27 USPQ2d 1510 at 1513.

In the instant disclosure, there is no reference made as to how and why a particular target protein is selected for expression or based on what structural or size characteristics. Perhaps, such guidance is lacking because the mechanisms or basis for enhanced solubility, with respect to test proteins that exhibit such a characteristics, is unknown. (Supra, Catalog, p. 8, ¶ 2). In addition, Applicant asserts that the specification teaches that various target proteins ranging from 150 to 400 amino acids are tested. (Remarks, p. 25, top ¶). However, as noted above, the exemplary test target proteins merely highlight that expression may or may not result in enhanced solubility.

Applicant asserts that in regard to guidance in selecting and testing various peptide extension, proteins and host cell systems, experimentation is an accepted aspect of the art and commercial entities facilitate ease of experimentation. (e.g., Freimuth Declaration, pp. 3-4). However, the instant claims are directed to a very large number of potential combinations of the requisite structural elements. The commercial entities to which Applicant points make available three constructs to be utilized in a bacterial expression system. (Supra, Catalog, p. 8). Thus, one can hardly conclude that protein overexpression utilizing SETs constitutes mere routine experimentation, no matter the number of potential SETs (within the parameters set in claim 53, 62 and 90), no matter the identity of the target proteins and no matter the type of the host cell expression systems (e.g., cell culture, plant, as well as yeast, bacterial and insect).

With regard to the legal standard for "undue experimentation", *In re Wands* is clear, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* ...and as set out in the rejection above: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims" (8 USPQ2d 1400, page 1404). Thus, one cannot examine each factor individually to determine undue experimentation. Rather, the totality of the circumstances defined by the factors on whole should form the basis as to whether undue experimentation is required.

The present arguments appear to be Applicant's opinion of what is routine experimentation and not the legal analysis set forth in *In re Wands*. Moreover, the instant disclosure is examined in view of the art at the time of invention. Thus any subsequent material changes or discoveries cannot be incorporated into the instant specification as a matter of course. In sum, the in view of the reasons set forth above, the instant disclosure does not enable the full scope of the instant claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 53-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Rechsteiner et al. (US 5,366,871; see whole document; hereinafter the '871 patent).

This rejection is of record and repeated herein. A response to Applicant's argument is set forth immediately following the body of the rejection.

The claims are drawn to an expression vector encoding a fusion protein comprising a peptide extension and a protein of interest. This limitation is interpreted as broadly as reasonable in that where a fusion construct is taught having two distinct amino acid sequences in-frame, either sequence can constitute an extension or the protein of interest (e.g. A-B fusion, A can be an extension while B is the protein of interest or vice versa). Furthermore, net charge is interpreted to mean the sum of the basic and acidic charges, i.e., one positive and one negative based on the individual amino acid residues comprising the peptide. Peptide of interest is not restricted to any particular size, thus can be a protein or polypeptide.

The '871 patent teaches an expression vector to use in a cell where a peptide extension is linked to a gene of interest (e.g. Abstract; Fig 1). More particularly, the vector is an M13 vector encoding a fusion protein of an ubiquitin peptide extension in frame with a protein of interest – cRAS. (e.g. Fig. 1; col. 8, Example 1). Expression is observed in prokaryotes (e.g. col. 9, Example 2) or it can also be in eukaryotes (e.g. col. 13, Example 10). The vector contains a polylinker or multiple cloning site. (e.g. col. 8, l. 55). Furthermore, the ubiquitin peptide extension contains the amino acid residues Ser-Glu-Glu-Glu-Glu, which would necessarily have a net negative charge of –4, as it contains four acidic or negative side chains. Moreover, it is an intrinsic property of peptides in solution that if the pH ranges in solution is altered (e.g. by adding buffer to a solution) that the net charge for the peptide is changed (e.g. more or less

negative). In addition, the fusion construct comprises additional peptide extensions consisting of the amino acid sequence, Pro-Gly-Cys-Met-Ser-Cys-Lys-Cys-Val-Leu-Ser (e.g. col. 8, Example 1), as well as multiple other peptide extensions as represented by SEQ ID NOs: 1-9, each of which would inhere a different net negative charge.

For example, the peptide extension represented by SEQ ID NO: 4 would contain a net negative charge of –5. (e.g. col. 17, SEQ ID NO: 4). As noted above, an intrinsic property for any peptide sequence in a solution is that at different pH values the peptide has a different net charge. Therefore, the various peptides taught in the '871 patent could intrinsically contain a different net negative charge. Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the peptide extensions of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). In sum, the '871 patent anticipates the rejected claims.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant asserts that the peptide extensions are all linked to ubiquitin and not various proteins or polypeptides of interest. In addition, Applicant asserts that the expression vector was no expressed in eukaryote cells.

As to Applicant's first argument, the claims merely read on a protein of interest. Thus, any protein of interest anticipates the claim. It is of little moment that the protein of interest in each case is ubiquitin.

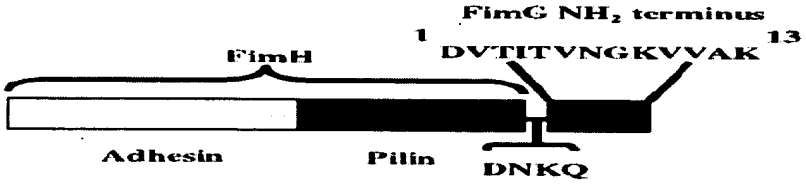
Regarding claim 55, the limitation "optimized for use with a eukaryotic cell" is not exclusively defined in the specification, other than to assert that such optimization is routine and well known in the art. Notwithstanding, the at least implied assertion, that claim 55 does not contribute anything over the prior art, the limitation is interpreted as broadly as reasonable to mean anything that is related to use of the vector with a eukaryotic cell. Regardless, it is respectfully pointed out that the claim is a product claim, thus any recitations of intended use for the product are of little moment with respect to patentability. In other words, there is no requirement to actually express the expression vector in a eukaryotic cell. Furthermore, as Applicant correctly points out the ubiquitin is modified to remove potential cleavage sites in eukaryotic cells, thus meet the limitation of *optimized for use with a eukaryotic cell.*

4. **Claims 53-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Barnhart et al. (PNAS. 2000; 97:7709-14; see whole document; hereinafter Barnhart).**

This is a new rejection. The claims are interpreted consonant with interpretations set forth above.

Barnhart teaches nucleic acid constructs in an expression vector that encode a fusion protein where a 13-amino acid peptide extension is added to the C-terminal end of a protein of interest. (e.g., Abstract; p. 7709, col. 2, ¶ 2, line 6). The peptide extension sequences are shown to enhance folding under physiological conditions in Gram-negative bacteria. (e.g., p. 7710, col. 1, ¶ 2; p. 7713, col. 1, ¶ 3).

As depicted in the figure below, the peptide extension comprises sequences (e.g., Aspartic acid, glycine), whereby under physiological conditions the net negative charge may fall between –2 and –22:



(p. 7710, Figure 1B).

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). In sum, the Barnhart anticipates the rejected claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

DANIEL M. SULLIVAN
PATENT EXAMINER